Pharmacy Update

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In This Issue

Estrogen Therapy for Osteoporosis Prevention in Postmenopausal Women

Menopause is accompanied by accelerated bone loss, and the central role of estrogen deficiency in postmenopausal osteoporosis is well established. Estrogen deficiency results in bone loss through its actions in accelerating bone turnover and uncoupling bone formation from resorption. In fact, annual decrements in bone mass of 3%-5% are common in the years soon after the menopause, and 0.5%-1% decrements are seen after 65 years of age. Observational studies suggest that ERT reduces the risk of spinal fracture by about 50% and of hip fracture by 30%. The reduction in fracture risk is greatest with higher estrogen doses and prolonged duration of use.

Estrogen replacement reduces bone turnover and increases bone density in postmenopausal women of all ages. Nonetheless, the protective effect persists as long as the treatment is maintained. With cessation of therapy, postmenopausal bone loss resumes at the same rate as that in untreated women. Ten years after HRT discontinuation, bone density and fracture risk were similar in women who had used ERT and those who had not. The ability of estrogen therapy to increase bone mass is enhanced by added androgens, calcium supplementation, and exercise. General protective measures, such as adequate calcium intake, regular weight-bearing exercise, and the avoidance of detrimental lifestyle habits such as smoking and alcohol abuse are appropriate for all women. Also, adequate exposure to sunlight is believed to protect against vitamin D deficiency, but many Western women are deficient in this vitamin. A determination of serum 25-hydroxy-vitamin D should be obtained in all women found to have osteoporosis.

Osteoporosis is a serious age-related disease that affects millions of women throughout the world. It is defined as a systemic skeletal disease characterized by low bone mass and microarchitectural deterioration with subsequent increase in bone fragility and susceptibility to fracture. Low bone density is the most important risk factor for osteoporosis.

According to the World Health Organization (WHO), a woman with bone mineral density greater than 2.5 standard deviations below the mean peak density has osteoporosis. Bone mass measurement accurately determines the bone density in the spine and the hip. The current "gold standard" method of bone density testing is dual-energy x-ray absorptiometry (DXA).

Osteoporosis affects approximately 28 million Americans and bears an economic burden of $14 billion per year. It results in approximately 1.5 million fractures in the U.S. each year. The annual fracture rate in women who are approximately 65 years of age is 1%-2%, whereas in women who are approximately 75 years of age it is 6%-10%. Furthermore, morbidity and mortality are significantly increased after an osteoporotic fracture. Of all the fractures due to osteoporosis (vertebral, hip, and wrist), hip fracture is the most serious. During the first year after an osteoporotic hip fracture, mortality is estimated at 23% and increases with age.

Currently, the management of osteoporosis incorporates efforts both for prevention and treatment. There are several agents approved by the U.S. Food and Drug Administration (FDA) for the prevention and treatment of postmenopausal bone loss: estrogen (for prevention and treatment), alendronate (5 mg daily for prevention; 10 mg daily for treatment), raloxifene (for prevention), and calcitonin (for treatment). Estrogen, however, is the treatment of choice. Natural and synthetic estrogens exert a positive effect on bone mineral density in a dose-dependent fashion, independent of age and mode of administration. Treatment can begin several years after the menopause without loss of efficacy in reducing fracture risk.

The decision, however, to start and continue hormone therapy is greatly influenced by the clinician's awareness of bone density evaluations and their clinical utility. The National Osteoporosis Foundation (NOF) recommends routine bone density testing for all women 65 years of age or older and for younger women who have clinical risk factors and have met criteria for treatment based on T-scores. The clinical risk factors emphasized by the NOF are 1) personal history of low-trauma fracture after age 45, 2) a family history of osteoporosis, 3) current cigarette smoking, and 4) low body weight. Other risk factors such as the use of glucocorticoids are also important. NOF recommends intervention with pharmacologic agents for osteoporosis for all women with T-scores of –2.0 and below and for women with T-scores of –1.5 to –2.0 who also have risk factors. The age at which treatment should be initiated has not been established clearly. A recent cross-sectional study suggests that women starting HRT later in life achieve a similar degree of bone preservation as those who start at the time of menopause. On the other hand, in the study of osteoporotic fractures, significant protection from hip fracture was found only among women who began HRT within five years after menopause—and not among women who began later.

An 8-year prospective study suggested that HRT has a more pronounced effect on the axial bone mass than that of the peripheral skeleton. This is most likely due to the relatively high turnover in vertebral bodies, consisting mainly of trabecular bone as compared with the predominantly cortical femur bones. The standard bone-sparing daily estrogen dose is equivalent to 0.625 mg of conjugated equine estrogen.

The Postmenopausal Estrogen/Progestin Interventions (PEPI) trial illustrates the favorable effects of estrogen on bone following the onset of menopause. This randomized, double-blinded, placebo-controlled trial studied 875 healthy postmenopausal women between the ages of 45 and 64 years. They were randomized to one of the following treatments in 28-day cycles: (1) placebo; (2) 0.625 mg of conjugated equine estrogen continuously plus 10 mg of medroxyprogesterone acetate for 12 days; (3) 0.625 mg of conjugated equine estrogen plus 2.5 mg of medroxyprogesterone acetate continuously; or (4) 0.625 mg of conjugated equine estrogen continuously plus 200 mg of micronized progesterone for 12 days. Overall, women assigned to HRT, regardless of the regimen, had significantly higher bone mineral density in both the hip and the spine at the 36-month evaluation compared with those assigned to placebo. Active HRT resulted in mean total increases ranging from 3.5% to 5% in spinal BMD and approximately 1.7% in hip BMD.

The recommended daily intake of elemental calcium is 1000 mg for premenopausal women and postmenopausal women who are taking estrogen replacement, and 1500 mg for postmenopausal women who are not taking estrogen replacement. To achieve this amount of calcium, most women require supplementation to their dietary intake.

Even low doses of estrogen may increase bone mass when they are supplemented with adequate calcium intake. A recent randomized controlled study showed that 0.3 mg of esterified estrogen administered along with adequate calcium (1000 mg/d of elemental calcium) prevented bone loss in postmenopausal women. Furthermore, for elderly women, continuous low-dose HRT combined with adequate calcium and vitamin D prevented bone loss. A 25 mcg/day estradiol transdermal system is now approved for osteoporosis prevention as well as for treating menopausal symptoms.

For women at high risk for osteoporosis who have contraindications for HRT, alternative regimens including raloxifene, the bisphosphonates, and calcitonin. Raloxifene (60 mg daily) is approved by the FDA for postmenopausal osteoporosis. The MORE study showed that raloxifene substantially decreases the vertebral fracture risk in postmenopausal women (relative risk using 60 mg of raloxifene daily is 0.7; relative risk using 120 mg of raloxifene daily is 0.5). This study also showed that the frequency of vertebral fractures was reduced both in women who had preexisting fractures and those who did not. However, the risk of nonvertebral fracture for raloxifene versus placebo did not differ significantly. Regardless, clinical trials have shown greater effects on bone mineral density with ERT than with raloxifene.

The bisphosphonates are also useful alternatives to HRT. Biphosphonates are analogues of pyrophosphate that inhibit bone resorption. Drugs in this class include alendronate, etidronate, pamidronate, risedronate, and tiludronate. Alendronate is the first biphosphonate approved by the FDA for treatment of osteoporosis. Alendronate has no known impact on the incidence of cardiovascular disease or breast or endometrial cancer. It should be noted that estrogen administration along with bisphosphonates produces greater gains in bone density than either agent alone.

Treatment with salmon calcitonin results in increased spinal bone density, but this effect is less than that seen with estrogen or the biphosphonates. Nasal calcitonin (200 IU daily) also has been shown to reduce the risk of new vertebral fractures in postmenopausal women with osteoporosis.

References available upon request

Levetiracetam (Keppra®): A Brief Review

Indication

Levetiracetam is approved as adjunctive therapy in the treatment of adult patients with partial-onset seizures.

Pharmacology

Levetiracetam is a pyrrolidone derivative that is chemically unrelated to other anticonvulsant medications. Its antiepileptic activity is thought to occur via a novel pathway that does not appear to effect known mechanisms of inhibitory and excitatory neurotransmission. EEG recordings of hippocampal epileptiform activity have shown that levetiracetam appears to prevent seizure propagation by stabilizing neuronal cell membrane potentials without causing hyperpolarization.

Pharmacokinetics

The bioavailability of levetiracetam approaches 100% and is unaffected by food, antacids, or the size of the dose. Peak drug concentrations, C_{max}, and area under the curve (AUC) concentrations display linear kinetics, in healthy volunteers. Plasma protein binding of levetiracetam and its major inactive metabolite is less than 10%. The average volume of distribution in a 70-kg human is between 35 and 49 L, indicating that levetiracetam is distributed into extracellular fluids. Approximately 35% of each dose of levetiracetam is metabolized via cytochrome P450 independent enzymatic hydrolysis to an inactive carboxylic acid metabolite. Therefore, levetiracetam is not subject to induction or inhibition by other drugs. Two other inactive metabolites account for less than 3% of the administered dose. Neither the primary metabolite of levetiracetam nor levetiracetam undergoes enantiomeric interconversion. Levetiracetam is primarily eliminated in the urine as the parent drug (~66%) via first-order elimination. Renal and total clearance of levetiracetam and its carboxylic acid metabolite are directly proportional to creatinine clearance and both are readily removed by hemodialysis. Renal elimination of the carboxylic acid metabolite of levetiracetam is decreased by coadministration of probenecid. Elimination of levetiracetam and its metabolites in feces is negligible. The half-life of levetiracetam is approximately 7 hours in adults who have normal renal function.

Selected Clinical Trials

Patients were eligible to participate in the three pivotal trials if they were at least 16 years of age, experienced a minimum of one seizure per week despite a stable regimen of one or two antiepileptic drug(s), and if they had at least a 2-year history of partial seizures. Exclusion criteria for the studies included the following: current use of medications with CNS activity (concomitant use of one or two antiepileptic drug(s) was mandatory for study inclusion); a history of drug or alcohol abuse; weight less than 50 kilograms; clusters of partial seizures during the baseline period; the display of either suicidal tendencies or psychiatric illness which required treatment; or who were not otherwise in general good health.

The primary measure of effectiveness in all three studies was the mean or median percent reduction in weekly partial seizure frequency during the titration and maintenance periods. The number of patients with >50% reduction from their baseline seizure frequency was the secondary endpoint.

Cereghino and coworkers conducted a multi-center, parallel-group, double-blind, randomized, controlled trial to compare the difference in efficacy of levetiracetam to placebo in the treatment of adult patients who had partial seizures which were refractory to the use of one or two other antiepileptic drugs. Two hundred ninety-four patients, 62% of whom took two antiepileptic drugs, were randomized to one of three treatment arms after a prospective 12-week baseline period. The treatment arms were levetiracetam 500 mg, given orally, twice daily, plus a maximum of two concomitant antiepileptic drugs (n=98); levetiracetam, 1,500 mg, given orally, twice daily, plus a maximum of two concomitant antiepileptic drugs (n=101); or placebo, given orally, twice daily, plus a maximum of two concomitant antiepileptic drugs (n=95). A 4-week titration period ensued after which patients were followed for 14 weeks. Both primary and secondary outcome measures included the titration and maintenance periods (See Table 1).

Shorvon and colleagues conducted a randomized, placebo-controlled, double-blind, multi-center cross-over trial to assess the effectiveness of levetiracetam in the treatment of adult patients who experienced partial seizures that were resistant to the use of one or two other antiepileptic drugs. Three hundred twenty-four patients participated in this trial. Two hundred forty-seven (76%) were also taking two antiepileptic drugs. The patients were randomized to one of three treatment arms after an 8- to 12-week prospective baseline period. The treatment reimens were levetiracetam, 500 mg, given orally, twice daily, plus a maximum of two concomitant antiepileptic drugs (n=106); levetiracetam, 1,000 mg, by given orally, twice daily, plus a maximum of two concomitant antiepileptic drugs (n=106); or placebo, given orally, twice daily, plus a maximum of two concomitant antiepileptic drugs (n=112). After a 4-week titration period, the patients were followed for 12 weeks. Both primary and secondary outcome measures included the titration and maintenance periods (See Table 1).

Table 1. Summary of Results from the Pivotal Trials

	Cereghino	Shorvon	Ben-Menachem
Primary Endpoint	***Median***	***Mean***	
1,000 mg/day	26.1% (n=98)	17.1% (n=106)	NA
2,000 mg/day	NA	21.4% (n=106)	NA
3,000 mg/day	30.1% (n=101)	NA	23.0% (n=181)
Secondary Endpoint*			
1,000 mg/day	29.7% (n=98)	14.5% (n=106)	NA
2,000 mg/day	NA	28.9% (n=106)	NA
3,000 mg/day	32.2% (n=101)	NA	25.0% (n=181)
Placebo	**7.4% (n=95)**	**6.3% (n=112)**	**14.4% (n=105)**

Primary endpoint: percent reduction in weekly partial seizure frequency during titration and maintenance periods
Secondary endpoint: number of patients with > 50% reduction from their baseline seizure frequency
* Placebo rate removed

Ben-Menachem and associates conducted a randomized, double-blind, placebo-controlled, multi-center trial that evaluated the efficacy of levetiracetam in the treatment of partial seizures in adult patients that were resistant to the use of one other antiepiletic drug. Two hundred eighty-six patients were randomized to one of two treatments after a prospective 12-week baseline period. The treatment arms were levetiracetam, 1,500 mg, given orally, twice daily, plus one concomitant antiepileptic drugs (n=181); or placebo, given orally, twice daily, plus one concomitant antiepileptic drugs (n=105). A 4-week titration period ensued after which patients were followed for 12 weeks. Both primary and secondary outcome measures included the titration and maintenance periods (See Table 1).

Adverse Reactions

During clinical trials, levetiracetam was studied in 769 patients as adjunctive therapy for partial seizures. During these trials, patients received either one or two concomitant AED(s). Adverse effects reported at a frequency of 2% when compared to placebo included somnolence (7%); asthenia (6%); dizziness (5%); infection (5%); ataxia (2%); depression (2%); emotional liability (2%); nervousness (2%); pharyngitis (2%); and vertigo (2%). Asthenia, somnolence, and dizziness appeared to occur predominantly during the first 4 weeks of treatment. Slow upward titration of the levetiracetam dose may help decrease the incidence of somnolence. Laboratory changes which occurred during clinical trials at a frequency of ≥ 1 % when compared to placebo included the following: leukopenia (1.4%) and neutropenia (1%).

Pregnancy/Lactation

Levetiracetam is rated as a pregnancy category C, based on the presence of teratogenic or embryocidal activity during animal studies. Levetiracetam has not been studied in pregnant women and has a pregnancy category C rating based solely on animal data. It is not known whether levetiracetam is excreted in human breast milk.

Contraindications

Levetiracetam is contraindicated in individuals with a prior history of a hypersensitivity reaction to levetiracetam or any of the inactive ingredients in Keppra® tablets.

Warnings

In controlled clinical trials, patients treated with levetiracetam developed either psychotic symptoms, psychotic depression, or attempted suicide at an increased frequency of 0.5% placebo-treated patients. One of these cases resulted in suicide. Levetiracetam-induced psychosis was seen during the first week of treatment and abated following treatment discontinuation. The reported cases of hallucination, psychotic depression, or attempted suicide either resolved or were not attempted again despite continued treatment. All of these cases occurred within the first 6 months of therapy.

Dosage and Administration

A definitive dose-response relationship has not been established in clinical trials. The recommended dose of levetiracetam as adjunctive therapy for partial seizures in adults is 1,000 mg, by mouth, per day, given as two divided doses. If an incomplete response is seen after 2 weeks, the daily dose can be increased by 1,000 mg at 2-week intervals until the maximal daily dose of 3,000 mg is obtained. Levetiracetam is only available as a tablet for oral administration. The dose of levetiracetam should be adjusted in patients with renal dysfunction according to the product labeling.

About 50% of the total body stores of levetiracetam is removed during a 4-hour hemodialysis session. Therefore, a 250 mg to 500 mg supplemental dose should be given at the end of each dialysis session. There is no need to adjust the dose of levetiracetam in patients with hepatic dysfunction.

Drug Interactions

The pharmacokinetics of levetiracetam were studied in humans when levetiracetam was coadministered with digoxin, warfarin, oral contraceptives, probenecid, and other antiepileptic drugs which included the following: carbamazepine; gabapentin; lamotrigine; phenobarbital; phenytoin; primidone; and valproic acid. No interactions of clinical significance were reported.

Conclusions

Levetiracetam appears to be effective and generally well tolerated as adjunctive treatment for adults with partial-onset seizures. The potential for serious interactions between levetiracetam and other medications is low, but patients should be cautioned that they may experience dizziness and somnolence while taking this drug.

References available upon request

Drug Information Service

- Patient-specific pharmacotherapy evaluation and management
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- You can receive immediate e-mail notification of new material as soon as it is posted on the MedWatch website. Just send a subscription message to *fdalists@archie.fda.gov*. In the message body enter: *subscribe medwatch* and your e-mail address.

Formulary Update

The Pharmacy and Therapeutics Committee recently approved the following formulary changes:

Additions

- Piperacillin/Tazobactam (Zosyn®), an injectable semisynthetic penicillin combined with a beta-lactamase inhibitor (use requires approval by the infectious diseases consult service)
- Pegylated Interferon Alfa-2b (PEG-Intron®), a long-acting, injectable preparation of a recombinant interferon for the treatment of chronic hepatitis C

Editor's Note

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